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KINGAN, TIMOTHY G				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

10/556,239

**Applicant(s)**

SCHNELLE ET AL.

**Examiner**

TIMOTHY G. KINGAN

**Art Unit**

1797

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 November 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-85/86)
- Paper No(s)/Mail Date 11/08/2005
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the phrase "...active segments alternate with the at least one reaction liquid and passive segments of a barrier liquid: " it appears from the specification that "reaction liquid" comprises active segments and passive segments/barrier liquid together; as worded, it appears that a component of the reaction liquid alternates with the reaction liquid itself. Applicant may have intended to alternate active segments and passive segments alone.

### ***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
3. Claims 1, 3, 5, 6, 9 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over G. Gradl et al., in Micro Total Analysis Systems 2000 pp. 443-446 (herein after Gradl) in view of W.B. Betts and A.P. Brown, U.S. Patent Application Publication 2003/0159932 (herein after Betts) and H.G. Wada et al., U.S. Patent 6,592,821 (herein after Wada).

For Claim 1, Gradl teaches an instrument for cell separation and a method of its use comprising a 3D microelectrode system for holding and kinetic analysis of single cells with optical detection techniques (abstract). Gradl further teaches loading cells by continuous flow in a channel (movement of at least one particle in the main channel up to a holding device) up to a "Loader" microsystem (p. 2, ¶ 1) (at least a temporary holding of at least one particle, such holding comprising contactless fixing with a holding force acting in contactless manner) supporting reagent change and washing (abstract) (supplying the reaction liquid from at least one lateral channel into the main channel so that a particle is rinsed) via channels oriented orthogonally to the main channel (Fig. 1, and as evidenced by H. Andersson and A. van den Berg, *Sensors and Actuators B* 92:315-325, 2003: see Fig. 3; examiner relies on the latter reference for its clear depiction of the arrangement of channels and electrodes for use in dielectrophoresis of particles).

Gradl does not teach the holding device arranged downstream after a mouth of the lateral channel. Betts teaches a method and apparatus for analyzing low concentrations of particles employing an AC electrokinetic technique [0003] (dielectrophoresis) and further teaches the advantages of including a step of focusing particles prior to a second holding electrode array for purposes of enhancing subsequent detection [0022], and that such focusing may be accomplished by hydrodynamic means with compression of solutions into narrow streams [0023], the focusing comprising a narrowing produced by the channel wall [0022]. It would have been obvious to one of ordinary skill in the art to use the step of hydrodynamic focusing according to the teaching of Betts, in the process of Gradl comprising dielectrophoretic holding of cells in order to attain the sorting benefits of hydrodynamic flow. Wada teaches a method of hydrodynamic focusing microparticles, an area of endeavor overlapping with that of applicant, such focusing comprising a "T-junction" or orthogonal intersection of two microchannels upstream of a detector (col 12, line 64 to col 13, line 16; Fig. 16). It would have been obvious to one of ordinary skill in the art to use the step of hydrodynamic focusing, according to Betts and in the context of dielectrophoretic holding of particles, by incorporating a lateral channel upstream of a detector alone, according to the teaching of Wada, or a detector couple with a holding device, in order to expand the range of focusing modalities available prior to caging and with expectation of success in improving the efficiency of capture within the holding device by positioning particles in closer lateral proximity to said device.

For Claim 3, Gradl and Betts do not teach a lateral channel for introducing reaction liquid, with a holding device downstream of said channel and on one side of the main channel, in order to provide for hydrodynamic focusing of particles downstream of the lateral channel, requiring the participation of the wall in physically restricting particles and prior to entry in the holding device/detection region. Wada teaches a "T-junction" or orthogonal intersection of two microchannels upstream of a detector (col 12, line 64 to col 13, line 16; Fig. 16) in the context of methods for attaining uniform flow velocity of particles in microfluidic systems (abstract), such methods comprising hydrodynamic focusing of cells to one side of a channel (col 2, lines 42-49) to overcome the limitations, in high-throughput assays, of non-uniform flow velocities (across the width of a channel) (col 2, lines 23-31). It would have been obvious to one of ordinary skill in the art to hold a particle to one side of the main channel in order to complement the use of hydrodynamic forces provided by flow from a side channel, which focus particles on one side of the channel, in order to provide for increased throughput by overcoming non-uniform flow velocity, according to the teaching of Wada.

For Claim 5, Gradl teaches use of negative dielectrophoretic forces for cell handling (p. 1, ¶ 3) and trapping (p. 2, ¶ 2) (the step of holding a particle in a holding device with dielectrophoretic forces).

For Claim 6, Gradl teaches the repelling force of negative dielectrophoresis in the presence of fluid flows of velocity 100  $\mu\text{m}$  per second (p. 2, ¶ 2 to p. 3, ¶ 1) (particle held by the holding device with a combination of dielectrophoretic and flow forces). Further, Betts teaches the step of improving or modifying the characteristics of

dielectrophoretic collection by narrowing or constricting the channel [0022] by creating a funnel arrangement produced by hydrodynamic focusing to compress solutions into narrow streams [0023] (use of dielectrophoretic forces with flow forces). It would have been obvious to one of ordinary skill in the art to use the combined dielectrophoretic and flow forces of Betts in order to attain the advantage of improved focusing or directing of particles to caging electrodes, according to the teaching of Betts.

For Claim 9, Gradl teaches the step of trapping single cells in a "Loader" micro system (holding device) followed by quantifying the fluorescence of cells using a CCD camera (p. 2, ¶ 1) (the step of taking at least one measurement on the particle in the holding device).

For Claim 11, Gradl, Betts and Wada do not teach washing in reaction liquid as alternating active and passive segments. However, it would have been obvious to one of ordinary skill in the art at the time of invention to use such segmentation in delivering active reaction liquid in order to provide passive segments during unloading of one particle and loading of the next, such steps occurring before beginning measurements. Further, one of ordinary skill would have found desirable such segmentation as a step in an automated method comprising replicate measurements with single particles in order to provide uniform timing and delivery of active and passive segments, and with reasonable expectation of improving precision in the measurements.

For Claim 12, Gradl, Betts and Wada do not specifically teach the position of particles with respect to the mouth of the lateral channel. However, Wada teaches particles at all positions with respect to the side channel, as particles are

hydrodynamically focused by flow from the lateral channel (Fig. 16). With regard to the position for caged particles, Gradl teaches reagent change for cell loading and washing could be achieved in less than 10 seconds (p. 3, ¶ 3); distances for dielectrophoretic caging with respect to the side channel is subject to optimization, based on the absolute and relative flow rates in the main and side channels, as well as the relative viscosities of fluids therein and the time required for cell loading and washing prior to entry in the holding device/detection region, such optimization being accessible to one of ordinary skill in the art.

For Claim 13, Gradl, Betts and Wada do not teach the timing of release with respect to holding and supply of reaction liquid. However, Gradl teaches reagent change for loaded cells (supplying of reaction liquid) and measurement of fluorescence over 5-30 minutes (p. 3, ¶ 3) (following loading). It would have been obvious to one of ordinary skill in the art, from such considerations, that release should take place after holding and supply of reaction liquid, since measurements following such events complete the cycle for a single particle.

For Claims 14 and 15, Gradl teaches sorting of cells according to their fluorescence with a potential yield of 100% (p. 3, ¶ 4; Fig. 3) (movement of particle into the main channel or the discharge channel based on fluorescence, a predetermined property).

4. Claims 2, 4 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gradl in view of Betts and Wada as applied to claims 1 and 6 above, and further in



view of T. Müller et al., Biosensors and Bioelectronics 14:247-256, 1999 (herein after Müller).

For Claim 2, Gradl, Betts and Wada do not teach the step of holding a particle on a local potential minimum. However, such step is known in the art of dielectrophoretic caging of single cells or particles. Müller teaches a dielectrical field cage comprising a symmetrical array of eight electrodes and its use in levitating (holding) a cell at the field (potential) minimum (p. 254, ¶ 2). It would have been obvious to one of ordinary skill in the art to use the step of applying a potential minimum of Müller in the process of Gradl, Betts and Wada in order to exploit the well known properties of negative dielectrophoresis for immobilizing particles, in contactless manner, for cloning, sorting or measurement.

For Claim 4, Gradl, Betts and Wada do not specifically teach the position in the main channel for holding the cell. Müller teaches particles directed with use of funneling electrodes for levitation in the center of the channel at a height of 20  $\mu\text{m}$  (p. 252, Fig. 6, caption). It would have been obvious to one of ordinary skill in the art to use the step of positioning in the center of the channel, according to the teaching of Müller in order to optimize use of channel width for a detection window.

For Claim 7, Gradl, Betts and Wada do not teach the step of a holding device generating a field barrier narrowing to a potential minimum. However, such step in use of dielectrical field cages is known in the art. Müller teaches a dielectrical field cage for trapping individual particles, the trap comprising funneling electrode elements which concentrate particles (p. 251, ¶ 3; Fig. 5b, F) (field barrier within the holding device

which narrows in the longitudinal axis). Müller further teaches that cells or particles, when trapped, are levitated in the field cage at the field minimum (the step of narrowing the barrier in the longitudinal direction to a local minimum). It would have been obvious to one of ordinary skill in the art to use the step of such narrowing within the process of Gradl, Betts and Wada in order to optimize the effectiveness of cell or particle capture by providing a cross sectional prefilter to direct flow toward the electrodes of the cage.

5. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gradl in view of Betts and Wada as applied to claim 6 above, and further in view of G.

Blankenstein, U.S. Patent 6,432,630 (herein after Blankenstein).

For Claim 10, Gradl, Betts and Wada do not teach the step of taking a reference measurement on a reference particle. However, use of such standard or reference cells or beads is known in particle separation and analysis art. Blankenstein teaches a system for particle separation and methods for its use comprising the step of separation of standard beads of different sizes (col 18, lines 59-62; col 22, lines 50-68). It would have been obvious to one of ordinary skill in the art to use the step of measuring the signal from standard particles in order to attain the well known benefit associated with calibration of an analytical system and the use of such calibration in quantitation associated with measurements on target particles.

6. Claims 8, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gradl, in view of Betts and Wada as applied to claim 13 above, and further in view of G. Fuhr et al., U.S. Patent 6,749,736 (herein after Fuhr).

For Claim 8, Gradl, Betts and Wada do not teach the field barrier generated by the holding device extending linearly and perpendicularly to the longitudinal axis of the channel. However, such orientation of electric fields formed by holding devices is known in the art. Fuhr teaches dielectrophoretic manipulation of particles in a channel (abstract) and the use of high-frequency electrical field generated in a channel vertical to the direction of flow (linear and perpendicular to the longitudinal direction of the channel) such fields structured to retard or position particles (act as holding devices) (col 4, lines 18-37). It would have been obvious to one of ordinary skill in the art to use a configuration or electrodes yielding a field perpendicular to the longitudinal direction in order to attain the potential with respect to funneling associated with such configurations.

For Claim 16, Gradl, Betts and Wada do not specifically teach deflection of a particle under the action of high-frequency electrical fields. However, such step is known in the art. Fuhr the deflection of suspended particles into adjacent channels by means of high-frequency electrical fields (col 9, lines 1-8). It would have been obvious to one of ordinary skill in the art to use high-frequency manipulation of particles in the method of Gradl, Betts and Wada in order to make use of differences in dielectric properties of cells that would be expected to exist in a heterogeneous population of cells

or in a population of cells that differ by virtue of treatment with a reaction fluid, such as in loading with fluorescent dyes.

For Claim 17, Gradl, Betts and Wada do not teach the step of separating a lateral channel from the main channel by a field barrier. However, the step for directly particle flow with field barriers, toward one channel in avoidance of a second channel, is known in the art. Fuhr teaches the step of using a barrier field, implemented by placement of microelectrodes extending into channels or at a bifurcation of two channels (Fig. 14, **27a** and **27b**), the second microelectrode serving to deflect large particles from entering the branching-off channel **29a** and instead directing entering to branch point **29b** (col 13, lines 42-48; Fig. 14). It would have been obvious to one of ordinary skill in the art to use the field barrier of Fuhr in the process of Gradl, Betts and Wada in order to attain the known advantage of directing particles to desired paths and preventing their entry into undesired paths.

7. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gradl in view of Betts and Wada as applied to claim 1 above, and further in view of S. Fiedler et al., Anal. Chem. 70(9): 1909-1915, 1998 (herein after Fiedler).

For Claim 18, Gradl, Betts and Wada do not teach a field barrier generated upstream of the holding device. However, such elements are known in the art. Fiedler teaches dielectrophoretic systems for sorting particles (title) comprising electrodes which form planar funnels that deflect particles by means of a field barrier upstream of a field cage (p. 1912, ¶ 2; Fig. 2) (a field barrier on the upstream side of the holding

device). It would have been obvious to one of ordinary skill in the art to use the barrier generated by the planar funnels of Fiedler in the process of Gradl, Betts and Wada in order to provide the well known advantage of field barriers for aligning particles prior to entry into negative dielectrophoretic holding devices.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY G. KINGAN whose telephone number is (571)270-3720. The examiner can normally be reached on Monday-Friday, 8:30 A.M. to 5:00 P.M., E.S.T.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TGK

/Jill Warden/  
Supervisory Patent Examiner, Art Unit 1797